#19

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Raju Kucherlapati, et al.

Serial No.: 08/031,801 Group Art Unit: 1804

Filed: 15 March 1993 Examiner: S. Ziska

For: GENERATION OF XENOGENEIC ANTIBODIES Attorney Docket No.: 7639-031-999

COMMUNICATION

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This communication is being mailed in response to a telephone conversation with Richard Schwartz, Biotechnology Specialist for Group 1800. The telephone conversation took place on November 9, 1995. The telephone conversation was in response to a recent telephone communication between Examiner Ziska and Applicants' representative, Albert P. Halluin. Examiner Ziska indicated that she would issue a new Office Action based upon information in the Supplemental Information Disclosure Statement submitted February 24, 1995 and the Communication filed February 23, 1995. Examiner Ziska had previously communicated to Applicants' representative that the application was to be placed in an interference. In view of the need to expedite prosecution, especially in view of the failure of the PTO to issue any Office Action in response to the amendment mailed December 23, 1994, Richard Schwartz agreed that the Applicants could submit a discussion of the

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being filed with the United States Patent and Trademark Office by facsimile transmission on November 16, 1995 (date) to facsimile telephone number (703) 305-3014.

Melissa L. Hilton 11-16-95
Date

6402

PEMP-46714.1

references prior to the preparation of an Office Action by the Examiner.

Applicants submit herewith a brief discussion of each of the publications submitted in the Supplemental Information Disclosure Statement of February 24, 1995 and the Communication of February 23, 1995. It is Applicants' position that rather than further delaying prosecution of the application, if the Examiner is of the view that the references are material, issues of patentability may be readily resolved in the interference proceeding as deemed appropriate by the parties.

1. Miller *et al.*, Nature 294:428-430 (1982). "Structural Alterations in J Regions of Mouse Immunoglobulin λ Genes Are Associated With A Differential Gene Expression".

Miller, *et al.* describes the discovery of a pseudogene in the mouse λ immunoglobulin gene complex. The mouse λ immunoglobulin gene complex comprises four different constant regions. Each constant region is associated with a separate J Region. Miller seeks to explain why only two of the four mouse immunoglobulin λ constant regions are expressed. Miller discovered that the J region associated with constant region 3, *i.e.* Jλ3, contains a natural mutation. This mutation is proposed to be the source of the failure of the λC3 Region to form productive recombinations with the variable region.

The research described in Miller does not alone, or in combination with any of the other publications of record, serve to render the claimed invention obvious. First, the claimed invention deals with a transgenic mammal comprising a modified genome. Miller, on the other hand, analyzes a naturally occurring mutation in a locus in the mouse genome. Additionally, the claimed invention is concerned with the immunoglobulin heavy chain subunit, whereas Miller is concerned with the λ light chain subunit. Furthermore, the claimed invention comprises a lesion in the J Region of the immunoglobulin heavy chain locus that prevents the locus from rearranging to produce a functional message encoding an immunoglobulin heavy chain subunit. Miller, on the other

643

hand, describes a lesion that does not prevent recombination of the entire locus, but instead merely prevents functional rearrangement of one of the four constant region genes.

2. Taketo, U.S. Patent 4,959,313

Taketo is solely concerned with the discovery of a novel cellular enhancer nucleotide sequence that can be used to increase expression of a gene of interest in an undifferentiated stem cell. This publication contains no discussion of gene inactivation, much less the inactivation of the heavy chain J immunoglobulin region. Rather than teaching gene inactivation, Taketo describes the use of the enhancer sequence to <u>increase</u> gene expression, and thus teaches away from the claimed invention.

3. Bertling, U.S. Patent 4,950,599

Bertling is concerned with a method of genetically modifying eukaryotic cells through a homologous recombination event with a polyoma virus derived vector. Bertling contains no suggestion that polyoma virus vector-mediated homologous recombination could or should be used to inactivate immunoglobulin genes, much less inactivate the J region of the heavy chain immunoglobulin genes. Furthermore, the gene modification technique described in Bertling is limited to those cells that are susceptible to infection by polyoma virus. There is no suggestion that polyoma viruses could be used to infect embryonic stem cells, fertilized oocytes, or any other cell type that is used in the production of transgenic mammals.

4. Yamamura, *et al.*, "Cell-Type-Specific and Regulated Expression Of A Human γ1 Heavy-Chain Immunoglobulin Gene in Transgenic Mice", <u>Proc. Natl. Acad. Sci., U.S.A. 83</u>:2152-2156 (1986).

Yamamura describes an experiment in which a rearranged human γ_1 heavy chain immunoglobulin gene was injected into a mouse egg so as to produce transgenic mice containing a rearranged human heavy chain gene. The human gene was shown

6464

to be expressed specifically in B cells and the regulation of the expression in B cells was shown to be inducible by injection of the transgenic mice with bacterial lipopolysaccharide. Production of the endogenous mouse heavy chains was not affected by the presence of the human gene. Thus, the research in Yamamura differs significantly from the claimed invention. The transgenic mammals of the claimed invention contain a genetic lesion in the J region that results in the inability of the locus to rearrange to produce a functional immunoglobulin heavy chain subunit. The transgenic mice described in Yamamura, on the other hand, are explicitly said to express a functional endogenous immunoglobulin heavy chain. Moreover, the J region is specifically targeted in the claimed invention, whereas Yamamura does not disclose any specific gene targeting.

5. Shimizu, et al., "Immunoglobulin--Isotype Expression By Trans-mRNA In A Human Immunoglobulin Transgenic Mouse" PNAS U.S.A. 86:8020-8023 (1989).

The experiments described in Shimizu describe the analysis of a transgenic mouse in which the transgene is a rearranged human μ transgene. The rearranged transgene serves to prevent rearrangement of the endogenous mouse immunoglobulin heavy chain locus through allelic exclusion. The point of the Shimizu paper is that about 4% of the transgenic animal spleen cells express a chimeric immunoglobulin comprising the human variable region from the transgene and an endogenous mouse constant γ_1 region. This publication does not discuss inactivation of the J region. Accordingly, this publication is not relevant to the patentability of the claimed invention because the claims state that the J region comprises a lesion that results in the inability of the immunoglobulin heavy chain locus to rearrange to produce a functional message encoding an immunoglobulin heavy-chain unit. There is no discussion in Shimizu of introducing any lesion into the J region.

645

6. Ayares, *et al.*, "Sequence Homology Requirements for Intermolecular Recombination In Mammalian Cells", Proc. Natl. Aca. Sci. USA 83:5199-5203 (1986).

This application describes a series of experiments in which homologous recombination between plasmids is measured. None of the recombination events described in this publication involve immunoglobulin genes or immunoglobulin gene derivatives. Furthermore, none of the cells in which recombination events are measured are useful for the generation of transgenic mammals. Additionally, gene inactivation is not even discussed. Accordingly, this publication appears to have no bearing on the issue of whether or not the claimed invention is obvious or anticipated by prior art.

7. Brinster, *et al.*, "Introns Increased Transcriptional Efficiency In Transgenic Mice", Proc. Natl. Aca. Sci. USA 85: 836-846 (1988).

The experiments described in this publication are designed to test the effect of introns on the expression of transgenes in transgenic mice. Brinster, demonstrated that the addition of introns serve to increase mRNA levels of the transgene tested. Brinster does not describe any genetic manipulations of immunoglobulin genes. Nor does Brinster describe the inactivation of any genes, let alone immunoglobulin genes. Accordingly, the claimed invention cannot be anticipated by Brinster.

8. Kucherlapati, *et al.*, "Homologous Recombination In Mammalian Somatic Cells", Prog. Nucleic Acid Res. Mol. Biol. 36:301-310 (1989).

This article it is an overview of homologous recombination in mammalian cells. Kucherlapati contains no discussion of how to inactivate immunoglobulin genes or even a suggestion why it would be desirable to inactivate immunoglobulin genes. As the claimed invention is directed to transgenic animals in which the J region of the immunoglobulin

gene contains a lesion that inactivates immunoglobulin gene rearrangement, it is clear that Kucherlapati cannot anticipate or render obvious the claimed invention.

Respectfully submitted,

PENNIE & EDMONDS

Dated: 11/16/95

Albert P. Halluin (Reg. No. 34,248 for 25,227)

1155 Avenue of the Americas
New York, New York 10036-2711
(415) 854-3660

Enclosure

6 47